Awards Spur Excellence in Research

Since the National Research Service Awards (NRSA) Program was enacted by Congress in 1974, the NIH has awarded institutional training grants to universities and research centers with the proven commitment and resources to nurture aspiring young scientists and train them for careers in biomedical, behavioral, and clinical research. As the NIH's primary means of supporting graduate and postdoctoral training, the since-renamed Ruth L. Kirschstein NRSA Program, now in its 30th year, seeks to prepare qualified individuals for careers that will have a significant impact on the nation's research agenda.

Inspired research. Through participation in the National Research Service Awards Program, the NIEHS supports the training of hundreds of emerging scientists who learn the skills and knowledge that will lead them to answer the most pressing research questions of today and tomorrow.

Program directors at the participating institutions—which are among the nation's top public and private research universities—select the trainees and develop a customized multidisciplinary curriculum of study and research experiences that together offer research training of the highest quality. Topics of study match areas of interest to the granting institute; at the NIEHS, these include molecular toxicology and epidemiology, neurotoxicology, toxicogenomics, biostatistics, bioinformatics, human and veterinary pathology, environmental health sciences, and occupational medicine.

"Topics of research are constantly evolving," says Carol Shreffler, who directs the program at the NIEHS. "Right now in the NIH, there is a big emphasis on interdisciplinary research."

In fiscal year 2003, as part of the NRSA Program, the NIEHS supported 49 institutional training grants totaling more than $19 million to fund 340 predoctoral and 106 postdoctoral trainees. The beneficiaries of the program are "the next generation of scientists," says Shreffler. "These are the new, young, vigorous individuals with innovative ideas who will carry on our research objectives in the future."

Groundwork for Growth

Each of the 49 NIEHS grantee institutions has a unique research focus, and all of them are known as trailblazers in their particular fields: "Whatever [research] they are doing, they are doing it better than anyone," Shreffler says. Trainees themselves are given the rare opportunity to work with and learn from faculty and principal investigators that are performing at the top of their fields.

During her postdoctoral fellowship at Vanderbilt University, former trainee Linda Distlerath, now vice president of global health policy for Merck and Company, studied the drug-metabolizing enzyme cytochrome P450. She and her colleagues sought to better understand the biochemical basis for genetic differences in drug metabolism and toxicity, and published a number of noteworthy papers, such as a 25 July 1985 report in the *Journal of Biological Chemistry* on potential polymorphisms involved in oxidative drug metabolism. "I feel very privileged to have been a part of that work—it was one of the seminal studies in the field at the time," she says. Distlerath still speaks reverentially of her mentor at Vanderbilt, Fred Guengerich. "He inspired high, high standards of quality, ethics, integrity, and validation of data," she says—standards she applies today at Merck.

Current trainee Christopher Toscano knew he wanted to conduct research that would advance science. Ultimately that desire brought him to the Johns Hopkins Bloomberg School of Public Health, where he is using animal models to study the molecular mechanisms of calcium signaling pathways that are short-circuited by lead exposure.

In particular, Toscano is studying *N*-methyl-D-aspartate (NMDA) receptor proteins present in the membrane of brain neurons. Lead binds directly to the NMDA receptors with a high affinity and inhibits their activation, causing the influx

Steve McCaw/Image Associates

of calcium—which normally occurs when the neuron fires—to decrease. Such decreases disrupt calcium signaling pathways, which can disrupt normal functioning of the neuron and contribute to learning and memory deficits seen in childhood lead exposure, Toscano explains.

Toscano says he is drawn to this research because it offers hope for prevention and reversal of lead-induced neurological defects. Five percent of U.S. children have elevated blood lead levels, and recently it has been shown that chelation therapy, the primary treatment for lead poisoning, does not reverse neurological problems caused by lead exposure, such as learning disabilities.

Equally passionate about using science to improve public health is Lacey Prouty, a graduate student in the Department of Epidemiology at the Harvard School of Public Health. Her community-based study focuses on immigrants of Caribbean and African descent, a population served by the Upham's Corner Health Center, which is partnering in the study. These immigrants live in a Boston neighborhood notorious for heavy, almost constant bus and truck traffic and the resulting diesel exhaust.

Prouty wants to clarify the health effects of breathing $PM_{2.5}$ (respirable airborne particulate matter measuring 2.5 microns or less in diameter), a diesel combustion by-product. To monitor these effects over a 48-hour period, study participants wear several devices, including an ambulatory electrocardiogram monitor, a monitor that collects a particulate sample on a filter, and a personal aerosol monitor that takes real-time measurements of particulate matter.

"Hopefully we'll be able to see a correlation between the particulates someone breathes into their lungs and actual physiological changes in cardiovascular function," Prouty says. By comparing results from healthy and unhealthy participants, she hopes to show clearly whether the health effects resulting from particulate exposure differ in patients who have underlying cardiovascular and respiratory conditions, such as high blood pressure or asthma.

Whereas Prouty's study involves a research approach grounded in observational human data collection, Charles Morton, a chemical engineer and Ph.D. candidate in molecular and systems toxicology at the Massachusetts Institute of Technology Biological Engineering Division, is busy applying fundamental engineering principles to the study of toxicology. He hopes his mathematical models will one day help toxicology and pharmacology researchers generate hypotheses, design experiments, and even streamline drug development while minimizing the need for human subjects.

Morton says the models could be used to study the fate of a molecule, from administration of or exposure to a toxic compound, to distribution to tissues through metabolism, to excretion—"imagine a toxic agent as a signal that enters the body and gets processed or metabolized, and the outcome is disease in the human body," he explains.

Many processes, such as binding kinetics, transport phenomena, and metabolism, are involved along the way. "If you can mathematically analyze the relationship between the input signal—the pattern of toxic exposure—and the output signal—the disease state—then you can figure out what's going on in between," Morton says.

Such models could be useful in explaining why different patient populations may be predisposed to developing disease following toxic exposures, or in making useful predictions of how individuals may respond to a drug, depending on their metabolic phenotype. Morton hopes researchers will one day use his models to explore systems ranging from exposure to environmental toxicants to drug–drug interactions.

Evolution of a Career

No one can say exactly where the work of Morton, Prouty, and Toscano will lead or where the trio of bright young scientists will end up, but it's clear that the training, teaching, and inspiration they are soaking up now will surely have far-reaching effects, for themselves and others. Just ask Distlerath.

Though she no longer conducts research in a laboratory, Distlerath does help lead Merck's efforts to address health issues in the developing world, especially concerning the global HIV/AIDS pandemic. She directs Merck's efforts to build relationships with public and private partners to develop and implement public health and educational programs. Among these are the company's partnership with the Bill and Melinda Gates Foundation to bring HIV/AIDS prevention, treatment, and care to Botswana, where more than 18,000 people are enrolled in the largest government-based

NIEHS Tops for Postdocs

The Scientist has named the NIEHS one of the best places for postdoctoral researchers to work in its annual survey, published 16 February 2004. Of the top 15 U.S. institutes, the NIEHS was voted third best.

The survey was open to scientists in the United States, Canada, Israel, and 18 European nations. More than 3,500 postdocs from over 900 institutions took the online survey. Respondents assessed their working environment according to 45 criteria under 11 broad topic areas: quality of training, quality of mentoring, quality of communication, value of the postdoctoral experience, quality of facilities and infrastructure, remuneration and compensation, availability of funding, information about work and funding opportunities, networking opportunities, family-related resources and support, and recreation and social opportunities.

According to Deborah Swope, director of the NIEHS Office of Fellows' Career Development, the NIEHS Trainees Assembly Steering Committee deserves most of the credit for the institute's high ranking. The assembly was started by fellows and graduate students at the NIEHS in order to foster the professional development of institute trainees. "The committee's hard work and dedication ensures that our fellows receive high-quality training," Swope says. "As a result, we now have a number of programs designed to enhance the professional development of NIEHS fellows. This means that our fellows not only receive excellent scientific training here, but also learn the skills that make them well-rounded, competitive scientists prepared for whatever career path they choose."

The survey results are available online at **http://www.the-scientist.com/postdoc/postdoc.htm. –Susan M. Booker**

AIDS treatment program in the African continent.

Lab days are also a thing of the past for former trainee Monica Cooper, although as a review chemist with the U.S. Food and Drug Administration (FDA) she keeps close tabs on other scientists' laboratory research as she previews new drug applications. The collaborative nature of the FDA's multidisciplinary review panels reminds Cooper of her trainee days at the Vanderbilt Center in Molecular Toxicology, where she studied how polycyclic aromatic hydrocarbons (by-products of combustion) react at certain sites in DNA, where they form adducts that can lead to carcinogenesis. "At the center, we did a lot of collaborative work with other labs and scientific disciplines, which has really helped me in my work at FDA," Cooper explains.

In contrast to Cooper and Distlerath, whose work has diverged from their initial scientific pursuits over the years, Nathan Cherrington is still conducting research in liver toxicity, which is roughly the same area that originally piqued his interest as a postdoctoral trainee at the University of Kansas Medical Center. "I never had any idea that what I was doing in graduate school would lead me to this," he says.

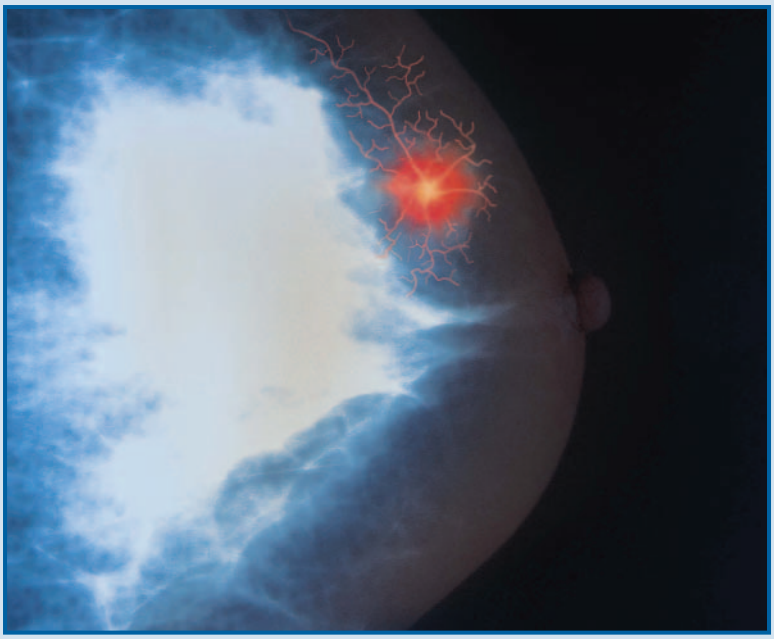
The same questions that fascinated Cherrington a few years ago as a trainee still command his attention today as an assistant professor in the Department of Pharmacology and Toxicology at the University of Arizona in Tucson. He's just taken them a step further.

As a trainee, Cherrington studied the regulation of hepatic transporters, agents that move toxic compounds across cell membranes, and discovered that normally occurring bioacids in the human body turn on a certain transporter known as multidrug-resistant protein. "Since then, I've been looking at the mechanisms of transcriptional regulation of that transporter," Cherrington says. "I'd like to see if some compound is able to upregulate the transporter to allow the liver to 'kick out' the toxic compound."

Cherrington, like so many other NRSA trainees past and present, has a passion to keep uncovering new answers to scientific puzzles and a willingness to tread new and difficult terrain to grasp them. That insatiable desire to keep searching for scientific answers, along with the tenacity to work hard and wait patiently—yet expectantly—for results, is just what the NRSA training grants are meant to inspire. **–Jennifer Medlin**

Headliners | Breast Cancer

NIEHS-Supported Research



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Estrogen Exposure and Metabolic Gene Expression

Ansell PJ, Espinosa-Nicholas C, Curran EM, Judy BM, Philips BJ, Hannink M, Lubahn DB. 2004. *In vitro* and *in vivo* regulation of antioxidant response element-dependent gene expression by estrogens. Endocrinology 145:311–317.

Exposure to chemicals that cause oxidative stress can contribute to the development of many diseases, including cancer. Many times, however, the metabolism of such chemicals has proven to be effective in modulating the degree of oxidative damage. In this paper, NIEHS grantee Dennis B. Lubahn and colleagues from the University of Missouri–Columbia explore how estrogen exposure affects enzyme expression during phase II of metabolism. Understanding how estrogens regulate phase II detoxification enzymes is important in explaining why estrogen exposure increases the risk of developing breast, ovarian, and uterine cancers.

The metabolism of many chemicals involves two distinct phases, each with characteristic enzymes. Phase I enzymes oxidize many chemicals, thereby forming intermediates. Phase II detoxification enzymes (such as glutathione-*S*-transferases and quinone reductase), which are responsible for metabolizing the products of phase I metabolic reactions, degrade these reactive intermediates by conjugation or reduction reactions, thereby protecting cells from oxidative DNA damage. Phase II enzyme expression is regulated by a DNA sequence known as the antioxidant response element.

The Missouri researchers sought to determine whether and how 17β-estradiol regulates gene expression that depends upon the antioxidant response element. Their results indicate that 17β-estradiol repressed glutathione-*S*-transferase gene expression. Additionally, glutathione-*S*-transferase and quinone reductase activities in the mouse uterus were significantly lowered in a dose-dependent manner following 17β-estradiol exposure.

The researchers conclude that 17β-estradiol and other estrogens can downregulate phase II enzyme activities in the uterus, thus potentially slowing the metabolism of reactive intermediates. This repression may increase cellular oxidative DNA damage that ultimately can result in the formation of cancer in estrogen-responsive tissues such as the breast and female reproductive organs. **–Jerry Phelps**

beyond the BENCH

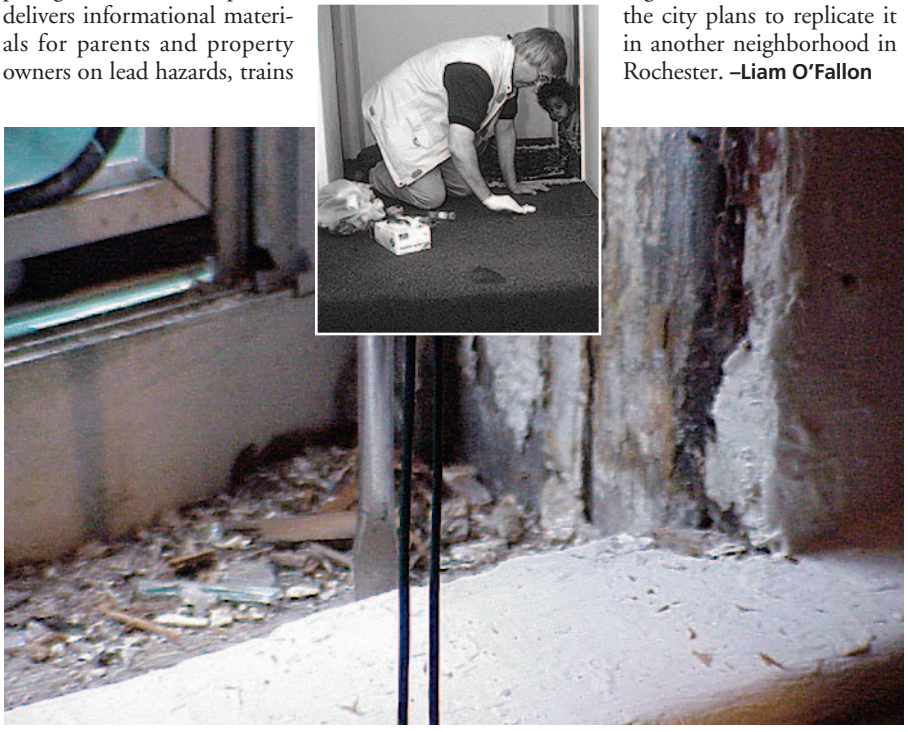
Go for the GLO

In Rochester, New York, where most of the housing stock was built before 1940, childhood lead poisoning rates in many neighborhoods surpass 35%. Health professionals consider childhood lead poisoning to be the greatest environmental health risk in the county, especially for children who live in low-income urban neighborhoods such as the Orchard Street community. Now some Rochester children at risk for lead poisoning are getting help from the Get the Lead Out of Orchard Street Community Houses and Kids (GLO) project.

GLO is coordinated by the Community Outreach and Education Program (COEP) at the University of Rochester Medical Center in collaboration with the Orchard Street Community Health Center (OSCHC), the Jay and Orchard Street Neighborhood Association, the Monroe County Department of Health, and the City of Rochester. The OSCHC initiated GLO in 2002 with the goal of preventing lead poisoning in children living in that community by inspecting homes of at-risk children, educating parents on how to protect their children from lead exposures, and encouraging landlords to fix lead hazards. The COEP conducts surveys with participating families, develops and delivers informational materials for parents and property owners on lead hazards, trains parents in lead-safe cleaning practices, and provides expertise in public outreach, education, and evaluation strategies.

Project members will eventually investigate the homes of 100 families with children who are patients at the OSCHC. Home assessments are initiated through well-child checkups, which has proven to be an effective strategy, with around a 90% participation rate. The project is unique in that it is preventive: most of the children involved do not yet have elevated blood lead, although they may live in homes where hazards are present. For those homes where lead hazards are found, GLO provides advocacy and support to tenants in interactions with property owners, and encourages property owners to apply for city and county funds to support lead remediation.

A key to GLO's educational efforts was creating a "lead lab" in an empty house with lead hazards typical of homes in the neighborhood. For two months, project members demonstrated to families, property owners, and local policy makers various low-cost techniques for safe lead cleanup, lead hazard reduction, and safe work practices. The lead lab was so effective in reaching diverse audiences that the city plans to replicate it in another neighborhood in Rochester. **–Liam O'Fallon**



Rich Kennedy, MD

Taking the lead on educating about lead. GLO teaches community members about the dangers of lead-based paint found in older housing, and shows families ways to determine if a hazard is present (for instance with a wipe sample, as in the inset), then safely remove it.